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Comparative Clinical Pharmacology of Gentamicin, Sisomicin, and Tobramycin

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Using a randomized crossover design involving 12 normal subjects, we studied comparatively the pharmacokinetics and tolerance of three aminoglycoside antibiotics, gentamicin, sisomicin, and tobramycin. Serum concentrations were determined during 8 h and the urine recovery rate was determined within 24 h after a 1-h intravenous infusion of the respective antibiotic in a dose of 1 mg/kg of body weight. Microbiological assay was performed with the agar diffusion test (*Bacillus subtilis*); pharmacokinetic calculations were performed by means of a digital computer on the basis of a mathematical model of an open, two-compartment system. Of the three antibiotics studied, gentamicin showed the lowest concentration in serum after termination of the 1-h infusion (3.85 ± 0.67 μg/ml), and the serum-regression curve steadily lay below those of the two other antibiotics. Sisomicin had the highest serum concentrations (4,66 ± 1.24 μg/ml) and the serum-level curve exceeded that of the two other antibiotics. Tobramycin occupied a position between sisomicin and gentamicin in form of its serum level characteristics. Corresponding to the serum kinetics we also found slight differences in the pharmacokinetic parameters, especially in serum half-lives, elimination constants, and areas under the serum level curves. The test of liver and kidney functions and the hematological systems, as well as the function of the stato-acusticus nerve, showed no pathological changes by any of the three antibiotics tested.

Caused by the increase in resistance of pathogenic bacteria, today infections with gram-negative germs, in intensive as well as hematologic and urologic wards, often mean chemotherapeutic problems. Thus the introduction of two new aminoglycoside antibiotics, sisomicin and tobramycin, could be a necessary extension of antibiotic attention facilities of those gram-negative infections.

Tobramycin was isolated, as factor 6, from the nebramycin antibiotic complex (21) and seems to be less toxic than gentamicin (2).

On the basis of several microbiological investigations (2-4, 7, 25, 28), an improved antibacterial effect can be seen for tobramycin, as compared to gentamicin, with regard to *Pseudomonas aeruginosa*.

Sisomicin is produced by fermentation of the new species *Micromonospora inyoensis* and has first been described by Weinstein et al. (27) and Wagman et al. (23). Sisomicin has demonstrated superiority in comparison to gentamicin and tobramycin by its better action in animal experiments with *Enterobacteriaceae* infections (3, 25, 26).

The following investigations compares both the pharmacokinetics and tolerance of three aminoglycoside antibiotics, gentamicin, sisomicin, and tobramycin.

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MATERIALS AND METHODS

Human volunteers. Six males and six females (23 to 59 years old; 46.5 to 80.5 kg [mean body weight 66.4 kg]; all healthy) were used in the 39 blood level studies of gentamicin, sisomicin, and tobramycin. None of the volunteers had received any antibiotic medication within the last 3 months.

Procedure for obtaining serum or urine specimens. Gentamicin (Refobacin; Fa. Merck, Darmstadt, Germany; lot G 3548), sisomicin (Schering Corporation USA/Bayer AG, Leverkusen, Germany; lot Pt 213017), and tobramycin (Gernebcin; Eli Lilly & Co, Hamburg, Gemany; lot CTI 2661/3 BB) were available in ampoule form. Ampoules of gentamicin contained 40 mg, ampoules of tobramycin and sisomicin contained 50 mg. Three ampoules of each charge were tested for their antibiotic contents by bioassay (twofold analysis); the average proven concentration of sisomicin was 103%, of tobramycin 101%, and of gentamicin 96% of the indicated dose.

The antibiotics were administered by a 1-h intravenous infusion of the respective antibiotic in a dose of 1 mg/kg of body weight. To achieve constant serum concentrations in due time, 70% of the dose was infused with an adjustable perfusor pump (Fa. Braun, Melsungen) in the first 10 min, and the rest of the antibiotic was steadily administered over 50 min. The antibiotic was solved in 50 ml of physiologic NaCl (Fa. Braun, Melsungen). For the infusion, to avoid repeated venipunctures, a scalp vein needle attached to a plastic catheter (Butterfly, Venofix, Ø 1.1 mm, Fa. Braun, Melsungen) was inserted into the forearm of each volunteer, and the catheter was filled with 0.9% NaCl (no heparin) through the reseal injection site. When drawing a sample, the first 3.0 ml of blood was discarded; 8 to 10 ml of blood was collected and allowed to clot, and after centrifugation, the serum was frozen with a freshly prepared standard at −20 C until the time for the bioassay (within a few days).

Using a randomized crossover design, we determined the serum concentrations during 8 h and the urine recovery within 24 h (three periods of collection) after the end of the 1-h infusion. Additionally, one serum value was received 30 min after beginning the infusion; puncture of a vein of the other arm permitted continuous infusion. Urine quantities were measured and small amounts, together with a recently prepared standard, were frozen at −20 C.

In three subjects, the renal clearance was determined for each antibiotic during a 4-h constant infusion, along with simultaneous measuring of the inulin clearance. After a loading of 0.7 mg of antibiotic substance per kg of body weight over 15 min, a constant dose of 1.2 mg/kg followed within the next 3.75 h. A 2% inulin solution (Deutsche Laevosan-Gesellschaft, Mannheim) was constantly administered by a perfusor-controlled parallel infusion after a fast 15-min starting infusion within 3.75 h, with a concentration of 20 mg/min. The inulin concentration was measured by the standard Antracen method.

Blood samples were taken at 30- to 60-min intervals during the infusion periods. Portions of urine were collected during 1.5 to 2 h and 3 to 4 h of the continuous infusion.

Before the clearance testing, the volunteers drank 1 liter of liquid each; during the infusion they received 400 ml/h each. Before all antibiotic administrations, normal serum and normal urine, generally free of activity, were collected from all volunteers.

In all test subjects, prior to the administration of the individual antibiotics as well as 24 h after the start of the experiment, biochemical examinations of liver and kidney functions, hematological parameters, and audiometric function were performed. Clinically, the local and general tolerance were observed as well as performing the Romberg and Nystagmus test.

Microbiological assay. The concentrations of the three tested aminoglycoside antibiotics were determined by the agar diffusion method with *B. subtilis* (ATCC 6633) as test organism and 1.5% Difco nutrient agar (17). The holes punched into the agar (13-mm diameter) were filled with 0.2 ml of serum or standard solution diluted in normal pooled human serum. Urine specimens were diluted 1/10 in 0.15 mol of Sörensen phosphate buffer, pH 7.8 for gentamicin and pH 8.0 for sisomicin and tobramycin.

The following charges were available as antibiotic laboratory substances: gentamicin with an activity titer of 622 μg/mg (Fa. Merck, Darmstadt); sisomicin with an activity titer of 598 μg/mg (Schering Corporation, Bloomfield, N.J.); and tobramycin, diluted as 1,010 μg of active base per ml of dilution liquid (Eli Lilly & Co., Indianapolis). Each agar plate contained a homologeous standard comprising four points and two test assays, each with a 1:2 and a 1:4 dilution ensuring a threefold determination for each assay.

The prediffusion time of 4 h was followed by 18 h of incubation at 37 C. The inhibition areas were determined by special measuring instruments, and the diameters were evaluated by half-logarithms against homologous standards.

With the method given, which has already been published (13), the lowest determinable levels were 0.03 μg/ml in buffer and serum for all three antibiotics.

Calculation of pharmacokinetic constants. Relevant pharmacokinetic parameters were determined by means of a Fortran program (method of least squares [5, 15]) developed by Koeppe and Hoeffler (11) using a digital computer on the basis of a mathematical model of an open two-compartment system (24).

The mathematical corrections apprised by Loo and Riegelmann (14) for the calculation of pharmacokinetic constants after intravenous infusion have been regarded.

Calculations and graphical data on an incremental plotter were obtained for every subject and for the mean regression curve of individual values. The parameters considered were: Y_t (micrograms per milliliter), concentration of the antibiotic in serum after 1 h of infusion; K_{el} (per hour), elimination rate constant of the central compartment; K_{12}, K_{21} (per hour), transfer rate constants between the central (V_1) and peripheral (V_2) compartments; $T_{50\%}$ (minutes), biological half-life as estimated from the β-phase of the serum concentration curve; cott (hour per micrograms per milliliter), "concentration times time" (11) area below the curve [Y(t)dt below the serum level curve]; rel V_D (e/100 kg), relative volume of distribution, calculated as

$$V_{Dss} = V_1 \cdot ([K_{12} + K_{21}]/K_{21})$$

Statistical evaluations were carried out using Student's t test.

RESULTS

Among the three aminoglycosides studied, gentamicin (Fig. 1, Table 1) showed the lowest concentration in serum (3.85 ± 0.67 μg/ml) after termination of the 1-h infusion. In the selected period, the regression curve corresponded to a relatively fast decreasing exponential elimination curve and the serum concentrations (Table 1) steadily lay below those of the other two antibiotics. The biological half-life (Table 2)

was 96 ± 24 min and the elimination constant was 0.43 ± 0.10 per h.

Sisomicin (Fig. 2, Table 1), on the other hand, had the highest serum concentration after the termination of the infusion (4.66 ± 1.24 μg/ml) and the serum level curve exceeded that of the other two antibiotics for the entire period of the study. The half-life (Table 2) was 122 ± 27 min and the elimination constant was 0.34 ± 0.13 per h.

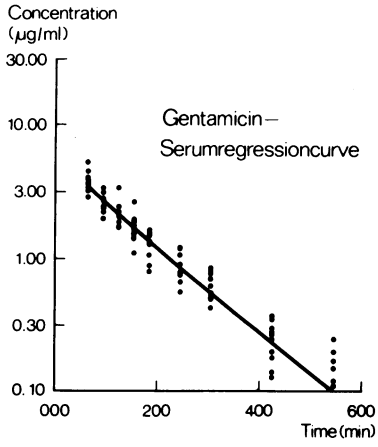

FIG. 1. *Regression curve and individual concentrations (micrograms per milliliter) of gentamicin in sera of 12 volunteers after 1-h infusion (1 mg/kg).*

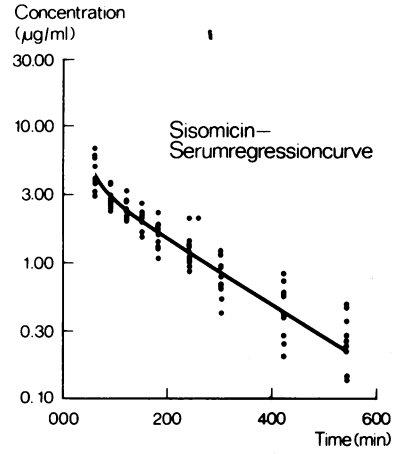

FIG. 2. *Regression curve and individual concentrations (micrograms per milliliter) of sisomicin in sera of 12 volunteers after 1-h infusion (1 mg/kg).*

TABLE 1. *Mean serum concentrations (with standard deviation) of gentamicin, sisomicin, and tobramycin at indicated times after 1-h infusion (1 mg/kg) in 12 volunteers*

Time (h)	Mean serum levels (μg/ml) after 1-h infusion (1 mg/kg)		
	Gentamicin (n = 12)	Sisomicin (n = 12)	Tobramycin (n = 12)
0.5	3.63 ± 0.71	4.26 ± 0.89	4.86 ± 0.90
1.0 (end of infusion)	3.85 ± 0.67	4.66 ± 1.24	4.40 ± 1.18
0.5	2.74 ± 0.38	3.19 ± 0.58	3.05 ± 0.54
1.0	1.10 ± 0.26	2.60 ± 0.42	2.40 ± 0.40
1.5	1.73 ± 0.40	2.07 ± 0.37	1.84 ± 0.34
2.0	1.27 ± 0.26	1.73 ± 0.36	1.47 ± 0.27
3.0	0.91 ± 0.26	1.30 ± 0.34	1.11 ± 0.21
4.0	0.62 ± 0.15	0.84 ± 0.24	0.72 ± 0.21
6.0	0.25 ± 0.09	0.47 ± 0.21	0.42 ± 0.16
8.0	0.12 ± 0.07	0.26 ± 0.13	0.20 ± 0.08

Tobramycin (Fig. 3, Table 1) occupied a position between sisomicin and gentamicin in terms of its serum level characteristics and showed, particularly 6 to 8 h after the end of infusion, higher concentrations than gentamicin. The biological half-life was 121 ± 18 min and the elimination constant was 0.35 ± 0.05 per h.

The synoptic graph (Fig. 4) in the form of a mean value curve of the original concentration once again demonstrates the serum kinetics of the three aminoglycoside antibiotics. Furthermore, the statistical test values of the Student's *t* test are to be taken from this graph, indicating the constant significant differences between the sisomicin and gentamicin concentrations.

Corresponding to the serum kinetics we also found differences in the pharmacokinetic parameters (Table 2). The serum half-lives of

TABLE 2. *Pharmacokinetic parameters of gentamicin, sisomicin, and tobramycin after 1-h infusion (1 mg/kg) in 12 volunteers*

Aminoglycoside antibiotic	Y_t (μg/ml) (end of infusion)	K_{el} (per h)	K_{12} (per h)	K_{21} (per h)	t_{50} (min)	cott (μg/ml per h)	rel V_D (0.1 kg)	Renal excretion (% of dose in 24 h)
Gentamicin	3.85 ± 0.67	0.43 ± 0.10	0.21 ± 0.20	0.76 ± 0.39	96 ± 24	14.6 ± 2.7	21.7 ± 4.6	69.4 ± 11.9
Sisomicin	4.66 ± 1.24	0.34 ± 0.13	0.88 ± 0.24	0.55 ± 0.39	122 ± 27	19.7 ± 5.8	17.1 ± 7.2	76.5 ± 9.8
Tobramycin	4.40 ± 1.18	0.35 ± 0.05	0.46 ± 0.30	0.61 ± 0.45	121 ± 18	18.1 ± 4.6	18.4 ± 5.2	74.3 ± 11.8

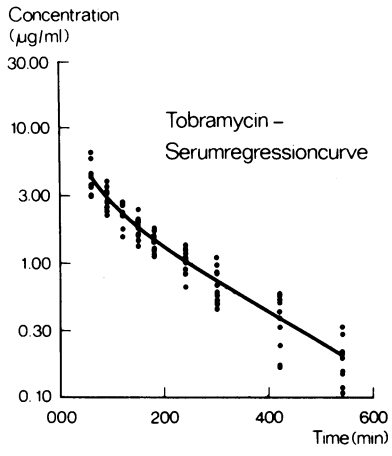

FIG. 3. *Regression curve and individual concentrations (micrograms per milliliter) of tobramycin in sera of 12 volunteers after 1-h infusion (1 mg/kg).*

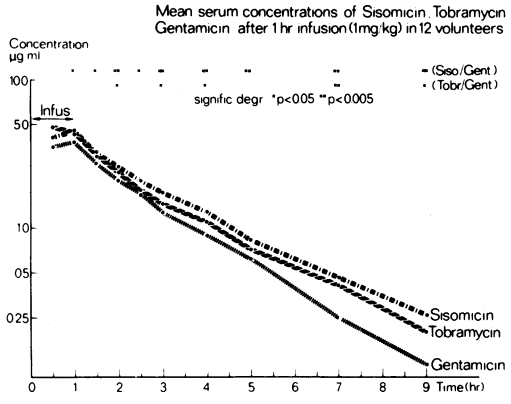

FIG. 4. *Mean serum concentrations (micrograms per milliliter) of drug for 12 volunteers after 1-h infusion of 1 mg of gentamicin, sisomicin, and tobramycin per kg.*

sisomicin and tobramycin are longer ($P < 0.01$), the elimination constants are correspondingly lower, and the areas below the serum level curves (cott) of sisomicin and tobramycin are larger ($P < 0.025$) than that of gentamicin. No essential differences are to be found with regard to the apparent volume of distribution which corresponds approximately to the size of the extracellular volume.

The 24-h-urine recovery rates of the three antibiotics (Table 3) showed no differences. Most of the administered doses were excreted within the first 6 h (61.9 to 65.5%) and the urine concentrations during this period moved from 70.0 to 303.0 µg/ml.

The clearance studies were performed in one subject whose average inulin clearances (which were tested simultaneously) lay at 113 ml/min per 1.73 m^2. Any difference in renal clearance could not be proved for the three antibiotics: gentamicin, 58.5; sisomicin, 66.5; tobramycin, 57.7 ml/min per 1.73 m^2 of body surface.

The tests of liver and kidney functions and the hematological systems, as well as the function of the stato-acusticus nerve, showed no pathological changes by any of the three tested antibiotics.

Also, in two subjects with moderate left-hand, side-high pitch absence, which had been audiometrically proved before the test began, no aggravation could be found during the entire test series.

The local and general tolerance of the three tested antibiotics was good.

DISCUSSION

The chemical structures and molecular weights of gentamicin (425), sisomicin (447), and tobramycin (468) do not essentially differ. Similarly, with all three antibiotics, as shown by the results of the studies from Gordon et al. (6) as well as Waitz et al. (25), no protein binding can be shown. It, therefore, is not surprising that the pharmacokinetic parameters obtained in this study for the three aminoglycoside antibiotics do not show any notable differences either. However, the mean serum concentrations of sisomicin always lay significantly above those of gentamicin. Yet this quantitatively only slightly marked difference in concen-

TABLE 3. *Urinary excretion of gentamicin, sisomicin, and tobramycin at indicated times after 1-h infusion (1 mg/kg) in 12 volunteers*

Aminoglycoside antibiotic	Urine concentration (µg/ml)			Urine recovery (%)			
	0–6 h	6–12 h	12–14 h	0–6 h	6–12 h	12–24 h	0–24 h
Gentamicin	250.0 – 79.5	26.4 – 3.5	5.0 – 0.6	61.9 ± 11.2	6.1 ± 2.7	1.4 ± 0.6	69.4 ± 11.9
Sisomicin	257.0 – 89.0	43.2 – 9.6	8.2 – 1.5	65.5 ± 9.3	8.2 ± 2.6	2.8 ± 1.0	76.5 ± 9.8
Tobramycin	303.0 – 70.0	31.5 – 4.8	6.4 – 0.7	65.1 ± 11.2	7.0 ± 3.6	2.2 ± 0.6	74.3 ± 11.8

tration when correlated to the minimal inhibitory concentration in treated gram-negative bacteria does not attribute a meaning in practical chemotherapeutics. In addition, this interpretation is supported by the scattered aminoglycoside concentrations observed by Riff and Jackson (19), as well as by Kaye et al. (9), during gentamicin therapy, for which they had no explanation.

Another important factor that must be considered for the characteristic of the differences in concentration between the three aminoglycosides is the differing contents of substance of the injected ampoules. The average concentration of the sisomicin ampoules lay at 7% above gentamicin; this would explain some differences in serum levels between these two antibiotics. Regamey et al. (18) have pointed to the consideration of these differing antibiotic charge concentrations of serum levels.

Today, the normal daily dose of tobramycin and gentamicin is 3 to 5 mg/kg and, in life-threatening infections, 5 to 8 mg/kg. Quick intravenous bolus injections should be avoided since, after 1 mg intravenously of gentamicin or tobramycin per kg, the concentration may surpass the toxicity limit of 12.5 to 15.0 μg/ml for a short period, as recently shown by Stratford et al. (22). On the basis of these reports and upon consideration of the 1.3 times higher vestibular toxicity of sisomicin (26), the relatively low dose of 1 mg/kg of body weight was selected and infused for 1 h. Regarding pharmacokinetic data for the individual aminoglycosides, the results obtained for gentamicin correspond entirely to those from previous studies of Black et al. (1), and Jao and Jackson (8), Winters et al. (29), as well as those of Naumann and Auwärter (17). The parameters of tobramycin kinetics correlate with the results obtained by Simon et al. (20), Regamey et al. (18), and Lockwood and Bower (12), whereas Naber et al. (16) reported longer biological half-lives and smaller apparent volumes of distribution. These authors (16), interpreting their results, point to the relatively high average age (69 years) of their subjects.

Significant differences in pharmacokinetics between tobramycin and gentamicin have not been shown by any author.

Concerning sisomicin, comparative pharmacokinetic factors do not yet exist. Our own investigations show that this aminoglycoside antibiotic possesses nearly the same pharmacokinetic parameters as tobramycin and gentamicin.

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